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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/876,252	06/07/2001	Dominic P. Behan	AREN-0240	8181

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COZEN O'CONNOR, P.C.
1900 MARKET STREET
PHILADELPHIA, PA 19103-3508

EXAMINER

BASI, NIRMAL SINGH

ART UNIT	PAPER NUMBER
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1646

DATE MAILED: 07/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/876,252

Applicant(s)

BEHAN ET AL.

Examiner

Nirmal S. Basi

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 June 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 101-144 is/are pending in the application.
- 4a) Of the above claim(s) 133-144 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 101-132 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission filed on 6/17/2004 has been entered.

2. Amendment filed 6/17/04 has been entered. Claims 1-100 are cancelled. Claims 133-144 withdrawn from consideration as being directed to a non-elected invention. Claims 101-132 are drawn to the elected invention of Group XXVIII.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action (3/25/03).

Claim Rejections - 35 USC § 101 and 35 USC § 112, 1st paragraph

4. Claims 101-132 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. Claims 101-132 remain rejected for reason of record as disclosed in Office Actions dated 3/25/03 and 12/17/03. Applicant's arguments, and the declaration of Dr. Behan have been fully considered and not found persuasive. Applicant's arguments and the declaration of Dr. Behan are addressed below. As an aside, it is noted that Dr. Behan is one of the inventors, and thus is a concerned party. Applicant and Dr. Behan argue:

a) The functionality of the non-endogenous constitutively activated version of GPR38 (V297K) is shared with that of the endogenous receptor (GPR38) and the skilled artisan would readily and immediately equate the functionalities of GPR38 with GPR38 (V297K),

b) A well established utility exists for GPR38 and, thus, for GPR38 (V297K). GPR38 (V297K) differs from GPR38 by a single amino acid and yields a constitutively active version of the endogenous receptor.

c) GPR38, which is expressed in the thyroid, has a well-established utility for the prevention of exacerbation of or treatment of Graves' disease. It was known at the time of filing that GPR38, which was disclosed as a GPCR, was expressed in the thyroid. Activation of GPR38 leads to increase in intracellular cAMP. An elevated level of intracellular cAMP in the thyroid leads to an over production of thyroid hormones in Graves' disease. It follows that an agent that inhibits a thyroid pathway leading to an increase in intracellular camp would have a well established utility for the prevention of exacerbation of or treatment of Graves' disease.

d) GPR38 (V297K) has a specific and substantial utility in that inverse antagonism of GPR38 (V297K) and by implication, GPR38, is useful in preventing or treating Graves' disease. GPR38 (V297K) can be used in an assay to identify an inverse agonist of GPR38.

e) The knowledge of the normal physiological role and endogenous ligand for GPR38 (and therefore GPR38 (V297K) is irrelevant to determining whether the claimed invention has utility.

Applicant's arguments have been summarized above (a-e). Applicant's arguments have been fully considered but not found persuasive. Examiner is not disputing that GPR38 and GPR38 (V297K) may both be G protein coupled receptors. Based on the record, there is not a specific and substantial asserted utility or a well-established utility for the claimed invention, GPR38 (V297K) or its related receptor GPR38. Applicant has asserted utilities for the specifically claimed invention of claims 101-132. Provisional application No. 60/123,945, pages 7, specifically states, that GPR38 is an orphan receptor, and "Gaining an understanding of the normal physiological role of [GPR38] will initially involve...identification of [its] endogenous ligand(s). Further, Provisional application No. 60/123,945, pages 7 and 8, specifically states, disclosed is that, "GPR38 has been reported to be closely related to the type 1 neurotensin receptor-1 and growth hormone secretagogue receptor of the GPCR, and is reportedly expressed in thyroid gland, stomach and bone marrow". Therefore, GPR38 is an orphan receptor for which the normal physiological role is unknown, and the endogenous ligand specific for that receptor has not been identified or is not known. As disclosed in the specification, GPCRs bind to a G protein (e.g. Gq, Gs, Gi, Gz, Go) and effect second messenger signaling which results in cellular activation or cellular inhibition. Gs stimulates the enzyme adenylyl cyclase, Gi (Gz and Go) inhibit this enzyme. Adenylyl cyclase catalyses the conversion of ATP to cAMP. The inhibition or stimulation of adenylyl cyclase affects cAMP levels in the cell. Cyclic AMP, in turn, drives gene expression by promoting the binding of a cAMP-responsive DNA binding protein or transcription factor that

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binds to the promoter at specific sites and drives expression of specific genes. There are many genes and proteins that are directly or indirectly regulated by changes in cAMP levels. On the other hand Gq and Go are associated with activation of enzyme phospholipase C, which hydrolyses PIP2, releasing intracellular messengers DAG and IP3. It is well established in the art that although GPCRs share the same common structural motif, they interact with specific G proteins and have divergent effects. The G protein that interacts with GPR38 is not known or disclosed. Does GPR38 couple to Gq, Gs, Gi, Gz or Go? The effect of activating or inhibiting GPR38 is not known and is further dependent on its associated G protein. The ligand for GPR38 is not known. The physiological function of GPR38 is not known. All GPCRs are not involved in the same disease state or dysfunction. There is no disclosure in the specification or prior art that discloses that GPR38 (V297K) or GPR38 is useful in preventing or treating Graves' disease. The agonist that interacts with GPR38 and decreases cAMP levels is not known. There is no disclosure that activation of GPR38 (V297K) or GPR38 leads to an increase in intracellular cAMP levels in Graves' disease. There is no disclosure that GPR38 (V297K) or GPR38 are over expressed or under expressed in Graves' disease. There is no disclosure that changing cAMP levels in a cell by modulating GPR38 (V297K) or GPR38 would have any effect on Graves' disease. It is not even known if GPR38 actually increases cAMP levels upon binding ligand. There is no disclosure of what specific effect inverse antagonism of GPR38 (V297K) and by implication, GPR38, would have on Graves' disease. Further, the utility of using GPR38 (V297K) to prevent

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or treat Graves' disease is not disclosed in the specification. The relationship of GPR38, cAMP levels and Graves' disease, relied on by applicant to argue utility, were not disclosed in instant application. Therefore for the reasons given above, using GPR38 to prevent or treat Graves' disease cannot be used to support utility in instant application.

The specification discloses general functional activities of G-protein coupled receptors (GPCR) which may be applicable to G-protein coupled receptors but does not disclose any activity associated with the specific GPR38 (V297K), of instant invention. As disclosed in the prior Office Action, the superfamily of G-protein-coupled receptors are highly divergent in their effects and include receptors for hormones, neurotransmitters, paracrine substances, inflammatory mediators, certain proteinases, taste and odorant molecules, and even photons and calcium ions. The GPR38 (V297K), of instant invention is considered by the examiner to be a member of the orphan receptor of G-protein coupled receptors i.e. seven transmembrane receptor with no known endogenous ligands. Further, a position that the GPR38 (V279K), is related, through homology, to known orphan receptors may be true, but the art shows it requires more than the disclosed homology to assign a function to an orphan receptor, knowledge of the endogenous ligand for the receptor is required.

The utilities asserted by Applicant are not specific or substantial. Since no specific function of the polypeptide of instant invention is known, and the hypothesized function is based entirely on conjecture from homologous polypeptides, the asserted utilities are not specific to instant polypeptide, but

rather are based on family attributes. Neither the specification nor the art of record disclose the GPR38 (V297K), fragments or variants thereof useful to identify drugs that affect said protein and modulate its activity. Similarly, neither the specification nor the art of record disclose any instances where disorders can be effected by interfering with the activity using the GPR38 (V297K), or related GPR38, or using fragments or variants thereof. Thus the corresponding asserted utilities are essentially methods of using GPR38 (V297K), to identify disease states associated with GPR38 (V297K), dysfunction and as targets for drug discovery. Therefore the asserted utilities are essentially methods of testing for or for potentially treating unspecified, undisclosed diseases or conditions, which does not define a "real world" context of use. Treating or testing for compounds that interact with GPR38 (V297K), which may be implicated in an unspecified, undisclosed disease or condition would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use. Since neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the claimed GPR38 (V297K), further experimentation is necessary to attribute a utility to the claimed polypeptides and fragments thereof. See *Brenner v. Manson*, 383 U.S. 519, 535–36, 148 USPQ 689, 696 (1966) (noting that "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing", and stated, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.").

Since neither the specification nor the art of record disclose any activities or properties that would constitute a “real world” context of use for the claimed GPR38 (V297K), further experimentation is necessary to attribute a utility to the claimed GPR38 (V297K). The instant application does not disclose the biological role of GPR38 (V297K), or its significance. The utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for the GPR38 (V297K), of the instant invention. The disclosed protein, whose cDNA has been isolated, is said to have a potential function based upon its amino acid sequence similarity to other known proteins. After further research, a specific and substantial credible utility might be found for the claimed isolated compositions. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicants claimed invention is incomplete. Assaying for ligands that may bind to GPR38 (V297K) or GPR38, both of unknown function, is considered further research and consists of its potential role as an object of use-testing.

Further, the rejection is based on the failure to disclose sufficient properties of the protein and/or polynucleotide to support an inference of utility. GPR38 (V279K), belongs is a family in which the members have divergent functions. Assignment to this family does not support an inference of utility because the members are not known to share a common utility. There are some protein families for which assignment of a new protein in that family would convey a specific, substantial and credible utility to that protein. For example,

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some families of enzymes such as proteases, ligases, telomerases, etc. share activities due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family.

The diversity of the biochemical function and the wide range of regulatory pathways involving GTP-binding proteins are well known in the art. Without some common biological activity for the family members, a new member would not have a specific, substantial, or credible utility when relying only on the fact that it has structural similarity to the other family members. The members of the family have different biological activities, which may be related to tissue distribution, but there is no evidence that the claimed compounds share any one of diverse number of activities. That is, no activity is known to be common to all members. To argue that all the members can be used for toxicology testing, diagnosis is to argue a general, nonspecific utility that would apply to virtually every member of the family, contrary to the evidence. Further, any compound could be considered as a regulator or modulator of tissue in that any compound, if administered in the proper amount, will stimulate or inhibit tissue. For example, salt, ethanol, and water are all compounds which will kill cells if administered in a great enough amount, and which would stimulate cells from which these compounds had been withheld, therefore, they could be considered regulators or modulators of tissue. However, use of these compounds for the modulation of tissue would not be considered a specific and substantial utility unless there was some disclosure of, for example, a specific and particular combination of

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compound/composition and application of such in some particular environment of use. Further, the specification does not disclose the significance of any test results, nor is there any evidence that the significance was known as of the filing date. If the expression of the claimed GPR38 (V297K) increases, is this a positive or negative outcome? Would this be a toxic response or not? The disclosure is insufficient to evaluate the results of the test in any meaningful manner.

Without knowing a biological significance of the claimed polypeptides, one of ordinary skill in the art would not know how to use the claimed invention in its currently available form in a "real world" manner based on the diversity of biological activities possessed by GTP-binding proteins. Contrast *Brenner*, 148 USPQ at 694 (despite similarity with adjacent homologue, there was insufficient likelihood that the steroid would have similar tumor-inhibiting characteristics), with *In re Folkers*, 145 USPQ 390, 393 (CCPA 1965) (some uses can be immediately inferred from a recital of certain properties) or *In re Brana*, 34 USPQ 1436, 1441 (Fed. Cir. 1995) (evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility; here, an implicit assertion of a tumor target was sufficiently specific to satisfy the threshold utility requirement).

The implication that the claimed invention has utility in testing, drug development and disease diagnosis/treatment, do not meet the standards for a specific, substantial, and or well-established utility for reasons set forth above.

In all cases a practical utility of an invention may be derived from belonging to a broad class of inventions. The requirement in any particular case, however, is that practical utility can be inferred if each and every member of the broad class possesses a common utility. The question in the instant application is whether the members of the family of proteins to which the claimed invention is structurally related have, individually, a specific, substantial and credible or well-established utility. Applicant has failed to show by a preponderance of the evidence, in enough detail, with respect to the described GPR38 (V297K), has any substantial use. The record shows that the GTP-binding protein family is diverse, and has such a broad definition, that a "common utility" cannot be defined. Moreover, the evidence of record is inadequate to determine the disease(s), drug(s) or toxicological screen(s) for which the compounds would be useful. In *Brenner*, the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible tumor-inhibiting effects and an adjacent homologue of the compound had proven effective. *Brenner*, 148 USPQ at 690. Here, there is no evidence that the claimed isolated compounds have any utility.

5. Claims 101-132 remain rejected under 35 U.S.C. 112, first paragraph, for reasons set forth in the Office Actions dated 3/25/03 and 12/17/03. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Since

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neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the claimed cDNA encoding GPR38 (V297K), further experimentation is necessary to attribute a utility to the claimed polynucleotide.

6. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 571-272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nirmal S. Basi
Art Unit 1646
July 7, 2004


BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600